Insights into the Use of CDK 4/6 Inhibitors in Patients with HR-positive Advanced or Metastatic Breast Cancer

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Abstract: Hormone receptor (HR)-positive breast cancer (BC) is the most common subtype of BC and some patients with such tumors experience recurrences. Endocrine-based therapy (ET) (e.g., tamoxifen, aromatase inhibitors (AIs), and fulvestrant) that has improved outcomes in such patients represents the initial therapy for women with HR-positive/human epidermal growth factor receptor 2 (HER2)-negative BC (considering no evidence of visceral crisis). However, the resistance to ET can occur in almost 50% of HR-positive BCs. In order to improve outcomes of patients with HR-positive metastatic BC, new treatment strategies are required. One such therapy is the new class of medications, cyclin-dependent kinase (CDK) 4/6 inhibitors, that have improved the outcomes in such patients (both endocrine-sensitive and endocrine-resistant).

This article presents evidence from the main clinical trials, which led to the approval of palbociclib, ribociclib, and abemaciclib. These three CDK 4/6 inhibitors have shown a significant improvement of the progression-free survival (PFS) in patients with HR-positive/HER2-negative metastatic BC when used in combination with selected ETs. In addition, some important patient management considerations, when choosing a particular CDK 4/6 inhibitor for an individual patient are presented. Furthermore, a need to find biomarkers for CDK 4/6 inhibitor sensitivity, efficacy, and resistance, to be able to precisely select the best patient-candidates for this treatment is highlighted.

Keywords: Hormone receptor (HR)-positive breast cancer (BC); metastatic BC; cyclin-dependent kinase (CDK) 4/6 inhibitors; palbociclib; ribociclib; abemaciclib; biomarkers

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1. Introduction

Hormone receptor (HR)-positive (e.g., estrogen receptor (ER) and/or progesterone receptor (PR)-positive) breast cancer (BC) is the most common subtype of BC (about 70% of all diagnosed BC)[1]. Such tumors are typically related with a better OS, and a possibility of late recurrences (e.g., up to 20 years)[2]. Endocrine-based therapy (ET) (such as tamoxifen, AIs, and fulvestrant) has contributed to better outcomes in patients with HR-positive advanced and metastatic BC. At present, ET represents the main initial therapy for women with HR-positive/human epidermal growth factor receptor 2 (HER2)-negative BC (considering no evidence of visceral crisis)[3]. Unfortunately, the resistance to ETs (e.g., de novo or acquired) may occur in almost a half of women with HR-positive BCs[4]. In fact, patients with breast tumors that are categorized as resistant to ET may have a relapse during adjuvant ET, or within one year after the end of therapy (EOT) (an early relapse)[4]. In contrast, patients with BC that are categorized as sensitive to ET (e.g., women, in whom a relapse occurs more than one year after the completion of adjuvant therapy) are considered to be more responsive to ET[3]. For women with very late recurrences (e.g., 10-20 years since treatment), endocrine resistance is rather unlikely[3, 4]. At this point, it is clear that optimizing the treatment for HR-positive BC requires new therapeutic strategies to overcome endocrine resistance. Recently, a new class of medications, the cyclin-dependent kinase (CDK) 4/6 inhibitors, has been shown to improve clinical
outcomes, in women with HR-positive/HER2-negative advanced and metastatic BC\(^5\).

This overview briefly presents profiles of three CDK 4/6 inhibitors, in pre- and post-menopausal patients, based on recent Randomized Controlled Trials (RCTs). Moreover, it indicates a need to identify biomarkers for CDK 4/6 inhibitor sensitivity, efficacy and resistance, so that clinicians will be able to precisely select the most appropriate BC patients for this novel treatment.

2. Breaking the Cell Cycle by Inhibiting the Cyclin D-CDK 4/6 Pathway – a Rationale for the Novel Therapeutic Target in Women with HR-positive BC

Neoplastic cells can avoid regulatory mechanisms of the mitotic cell-cycle and proliferate uncontrollably. The cell cycle includes the following phases: G0 (quiescence), G1 (pre-DNA synthesis), S (DNA synthesis), G2 (pre-division), and M (cell division)\(^6\). The progression from G1 to S is a key cell-cycle checkpoint (e.g., protecting the cell against abnormal replication, which is regulated by the cyclin D-cyclin-dependent kinase (CDK) 4/6-inhibitor of CDK4 (INK4)-retinoblastoma (Rb) axis)\(^6\). Unfortunately, malignant cells often overcome the Rb tumor suppressor protein (pRb)-dependent growth suppression, through phosphorylation and inactivation of pRb activity. Mitogenic signals (e.g., the Ras-mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways) enhance the accumulation of D-type cyclins in G1 phase, via the transcriptional and posttranscriptional mechanisms\(^6\). Activation of the cyclin D-CDK 4/6 complex leads to the hyperphosphorylation of the pRb, which inactivates its growth-inhibitory function. It should be underscored that the cyclin D–CDK 4/6–INK4–Rb axis is crucial for initiation of the cell cycle, and many cancers often disrupt this pathway by different mechanisms (e.g., mutation or amplification of CDK 4/6). For instance, amplification of the CCND1 gene, which encodes cyclin D1, has been identified in one to two-thirds of BCs\(^1, 6\). Furthermore, cyclin D1 protein overexpression is present in about one half of BCs\(^6\).

For the restoration of pRb-dependent tumor suppressor activity, in patients with HR-positive BC, inhibition of ER signaling and cyclin D-CDK4/6 activity is necessary. For this reason, the cyclin D-CDK4/6 pathway is such an important, novel therapeutic target for different pRb-positive cancer types (e.g., BC, non-small cell lung cancer, and melanoma)\(^6\). Importantly, in patients with HR-positive BC, the overexpression of cyclin D occurs frequently, and loss of pRb happens rarely. Therefore, the G1-to-S cell cycle checkpoint consists of a suitable target, and the CDK4/6 inhibitors, by addressing this key checkpoint, are able to prevent malignant progression\(^6\). The CDK 4/6 inhibitors have been found to improve outcomes in women with HR-positive/HER2-negative advanced and metastatic BC (both endocrine-sensitive and endocrine-resistant)\(^5\). Three selective CDK 4/6 inhibitors: palbociclib, ribociclib, and abemaciclib, have significantly improved the progression-free survival (PFS), in patients with HR-positive/HER2-negative metastatic BC, when used in combination with selected ETs\(^5\-15\).

3. HR-positive Metastatic BC

Hormone receptor (HR)-positive metastatic breast cancer (BC) refers to tumors that have receptors (R) for estrogen (E) and/or progesterone (P). Such tumors use estrogen for proliferation and distant spread. ER or PR positivity (e.g., expressed on the pathology report in percentages) is related to the likelihood of sensitivity to anti-estrogen medications. In these circumstances, an ET represents the targeted treatment for such tumors. Approximately 70% of BCs are HR-positive, and they usually occur in postmenopausal or elderly women\(^16\). Hormone receptors (HRs) represent complex structures that play the role of transcription factors, which may contribute to carcinogenesis. From a therapeutic point of view, the HRs may serve as both the targets and the possible predictors of response to ET. In practice, common examples of ET include selective ER response modulators (e.g., tamoxifen), aromatase inhibitors (AIs) (e.g., anastrozole, letrozole, or exemestane), ER down-regulators (e.g., fulvestrant), and luteinizing hormone-releasing hormone agents for ovarian suppression (e.g., leuprolide) (Table 1)\(^17\). In general, HR-positive BC has a good prognosis. However, there is still a risk of late relapse or metastases (e.g., several years after the initial BC diagnosis), and more than half of recurrences can occur over five years after the initial BC diagnosis (even in patients using ET)\(^18\). In almost a half of patients with HR-positive BC treated with adjuvant ET, a relapse eventually takes place\(^18\).

4. Resistance to Endocrine Therapy in Breast Cancer

The use of ET has been limited because of the tumor’s resistance. In addition, an increasing tumor burden can require another treatment modality, such as chemotherapy (CHT) that is often related with some toxicity.
resistance has been connected with overexpression or amplification of several genes involved in growth factor pathways (e.g., the ones mediated by epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER) family, such as HER-2, and HER-3, fibroblast growth factor receptor-1 (FGFR-1), and insulin-like growth factor receptor-1 (IGFR-1)). In particular, an abnormal activation of the main axis in the signaling system, which includes the phosphoinositide 3-kinase (PI3K)/AKT/mechanistic (mammalian) target of rapamycin (mTOR) growth and survival pathway, is related with ligand-independent ER activation. This ER activation triggers an activation of downstream pathways, which are not regulated by estrogen. Approximately 30% to 40% of HR-positive metastatic BCs have these types of mutations (e.g., an activating or gain-of-function types).

### 5. Deciphering Signals Involved in Endocrine Resistance in Patients with HR-positive BC

Abnormal cell proliferation in BC is often related to a hyperactive axis of the cyclin D-CDK 4/6. Oncogenic signals in HR-positive BC cause activation of CDK 4/6, leading to BC cells proliferation and phosphorylation of Rb gene. The cyclin D1-CDK 4/6 axis regulates cell cycle progression through phosphorylation and inactivation of Rb. It has been revealed that cyclin D1 gene amplification and/or protein overexpression can predict negative clinical outcome in a subgroup of women with HR-positive BC. Concurrently, it has been noted that the endocrine resistance is related to the enhanced cyclin D1 expression and Rb phosphorylation. In fact, this kind of resistance to anti-estrogen treatment has often been encountered in luminal B subtypes of BC.

### 6. Outcomes of Therapy with CDK 4/6 Inhibitors in Patients with HR-positive BC

Currently, it has been determined that the CDK 4/6 inhibitors can help fulfill the unmet needs of many patients with HR-positive metastatic BC. The CDK 4/6 inhibitors have an ability to block the activity of the cyclin D-CDK 4/6 holoenzyme. In this way, they can apprehend cell cycle progression (e.g., from the G1 to the S phase). In a consequence, using CDK 4/6 targeted medications inhibits the tumor growth and proliferation, in patients with HR-positive/HER2-negative advanced or metastatic BC. Moreover, it has been reported that the CDK4/6 inhibitors can prolong the time period until the development of endocrine resistance, in women with HR-positive/HER2-negative advanced or metastatic BC. In this way, CDK4/6 inhibitors have revolutionized the treatment strategies for such patients. Table 2 presents the evidence from the main clinical trials, which led to the approval of palbociclib, ribociclib, and abemaciclib. Moreover, the recent National Comprehensive Cancer Care Network (NCCN) guidelines have included the following therapeutic combinations: palbociclib with letrozole, palbociclib with fulvestrant, and ribociclib with letrozole, for postmenopausal women with HR-positive/HER2-negative advanced or metastatic BC.
**Table 2.** Progression-free survival upon CDK 4/6 inhibitor’s therapy, in women with HR-positive, HER2-negative metastatic breast cancer

<table>
<thead>
<tr>
<th>CDK 4/6 inhibitor</th>
<th>RCT acronym</th>
<th>FDA/EMA Approval Month, Year</th>
<th>Progression-free survival in the major CDK 4/6 inhibitor’s trials</th>
<th>Clinical implications</th>
<th>Author</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib</td>
<td>PALOMA 1</td>
<td>FDA Feb 2015</td>
<td>PFS favored a combination: palbociclib + letrozole; median PFS = 10.2 months for placebo + letrozole vs. 20.2 months for palbociclib + letrozole</td>
<td>Palbociclib in combination with letrozole is beneficial for the treatment of HR-positive, HER2-negative advanced BC in postmenopausal patients</td>
<td>Finn</td>
<td>2015</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>PALOMA 3</td>
<td>FDA Feb 2016</td>
<td>PFS (interim analysis) favored palbociclib (9.2 months vs. 3.8 months)</td>
<td>Palbociclib in combination with fulvestrant is beneficial for the treatment of HR-positive, HER2-negative advanced or metastatic BC with progression following ET</td>
<td>Turner</td>
<td>2015</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>PALOMA 2</td>
<td>FDA March 2017</td>
<td>PFS favored palbociclib (24.8 months vs. 14.5 months)</td>
<td>Palbociclib in combination with an AI for the treatment of HR-positive, HER2-negative advanced or metastatic BC in postmenopausal patients</td>
<td>Finn</td>
<td>2016</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>PALOMA 2</td>
<td>EMA Nov 2016</td>
<td>PFS was improved with palbociclib in combination with an AI or fulvestrant</td>
<td>Palbociclib in combination with an AI for the treatment of HR-positive, HER2-negative advanced or metastatic BC as initial ET, or palbociclib in combination with fulvestrant in patients who have received prior ET</td>
<td>Finn</td>
<td>2016</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>MONALEESA 7</td>
<td>FDA March 2017</td>
<td>PFS (interim analysis) favored ribociclib; ribociclib was also favored in the subgroup of patients with HR-positive, HER2-negative advanced BC at diagnosis</td>
<td>Ribociclib in combination with an AI as initial ET for the treatment of HR-positive, HER2-negative advanced or metastatic BC in postmenopausal patients</td>
<td>Hortobagyi</td>
<td>2018</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>MONALEESA 7</td>
<td>FDA July 2017</td>
<td>PFS was improved with ribociclib (median PFS = 23.8 vs. 13.0 months)</td>
<td>Ribociclib in combination with an AI as initial ET for premenopausal patients with HR-positive, HER2-negative metastatic BC</td>
<td>Tripathy</td>
<td>2018</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>MONALEESA 3</td>
<td>FDA July 2017</td>
<td>median PFS = 20.5 months for patients taking ribociclib compared to 12.8 months for those who received placebo</td>
<td>Ribociclib in combination with fulvestrant for postmenopausal patients with HR-positive, HER2-negative advanced or metastatic BC, as initial ET or following BC progression on ET</td>
<td>Slamon</td>
<td>2018</td>
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<tr>
<td>Ribociclib</td>
<td>MONALEESA 2</td>
<td>EMA August 2017</td>
<td>PFS was improved with ribociclib</td>
<td>Ribociclib in combination with an AI as initial ET for the treatment of postmenopausal patients with HR-positive, HER2-negative advanced or metastatic BC</td>
<td>Hortobagyi</td>
<td>2018</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>MONARCH 2</td>
<td>FDA Sep 2017</td>
<td>PFS was improved with abemaciclib; PFS = 16.4 months vs. 9.3 months</td>
<td>Abemaciclib in combination with fulvestrant for patients with HR-positive, HER2-negative advanced or metastatic BC with BC progression following ET</td>
<td>Sledge</td>
<td>2017</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>MONARCH 1</td>
<td>FDA Sep 2017</td>
<td>PFS was improved with abemaciclib; median PFS = 6.0 months; median OS = 17.7 months</td>
<td>Abemaciclib as monotherapy for patients with HR-positive, HER2-negative advanced or metastatic BC with BC progression following ET and prior CHT in the metastatic BC</td>
<td>Dickler</td>
<td>2017</td>
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<tr>
<td>Abemaciclib</td>
<td>MONARCH 3</td>
<td>FDA Feb 2018</td>
<td>PFS favored abemaciclib; benefits were observed across subgroups</td>
<td>Abemaciclib in combination with an AI as initial ET for the treatment of postmenopausal patients with HR-positive, HER2-negative advanced or metastatic BC</td>
<td>Goetz</td>
<td>2017</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>MONARCH 2</td>
<td>EMA Sep 2018</td>
<td>PFS was improved with abemaciclib</td>
<td>Abemaciclib in combination with an AI or fulvestrant as initial ET or in patients who have received prior ET</td>
<td>Sledge</td>
<td>2017</td>
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</table>

Abbreviations: CDK 4/6, cyclin-dependent kinase 4/6; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; AI, aromatase inhibitor; ET, endocrine-based therapy; PFS, progression-free survival; OS, overall survival; BC, breast cancer; CHT, chemotherapy; RCT, Randomized Controlled Trial

HER2-negative metastatic BC (Table 1)\(^{[17]}\).

### 7. Impact of CDK 4/6 Inhibitors on Current Practice Patterns

Certainly, CDK 4/6 inhibitors have revolutionized the therapeutic approach to patients with HR-positive/HER2-negative advanced or metastatic BC. In face of the dynamically changing treatment strategies for these patients, it is critical to know how such therapies should be applied in practice, and what factors may impact the treatment selection. These questions were addressed in a study that collected data from community oncology practice, in the US, via evaluating recent “real-world” therapy avenues in postmenopausal patients with HR-positive/HER2-negative metastatic BC\(^{[23]}\). The findings of this study revealed that in the first-line and second-line treatment, CDK 4/6 inhibitors were the most commonly used agents (e.g., 52.4% of patients received CDK 4/6 inhibitors in combination with AI (39.2%) or fulvestrant (10.0%) as first-line therapies). It should be noted that ET and CHT were also applied (in 30.2%, and 12.7% of patients, respectively), in the first line setting. According to data
from the physician’s questionnaire, about 60% of doctors reported that the CDK 4/6 inhibitors were the most commonly prescribed therapy for metastatic BC, due to their high efficacy and good tolerability. However, the universal treatment sequence for postmenopausal women with HR-positive/HER2-negative metastatic BC has not yet been established in practice. Therefore, physicians need to consider the clinical criteria for each individual patient, and use their best medical judgment.

8. The Importance of Biomarkers for Integrating the CDK 4/6 Inhibitors into Practice

It is important to mention that a lot of effort and resources have been directed into trying to identify biomarkers that can differentiate between patients, who would benefit from single-agent ET and those, who would need the combination therapy. Currently, these biomarkers have not yet been established. At present, ER-positive status is the best predictive biomarker to select BC patients for CDK 4/6 inhibitors therapy. Unfortunately, the recent RCTs, such as PALOMA-1 and MONALEESA-2, did not reveal predictive biomarkers that would be helpful in clinical practice. Until the biomarkers are identified, patients with HR-positive/HER2-negative metastatic BC, who have not previously received a CDK 4/6 inhibitor (or a combination therapy, including ET), can be started on palbociclib or ribociclib. Furthermore, abemaciclib has now been approved for use with fulvestrant, or as a monotherapy (e.g., in the pretreated patients with metastatic BC). A Possible Role of ctDNA in the Detection of Biomarkers for Patients with Metastatic BC

In metastatic BC, mutations usually develop slowly, as a response to the applied therapy. In result, the biology of the primary tumor may not be relevant to the metastatic setting. Therefore, in order to identify biomarkers of sensitivity or primary resistance to therapy, baseline metastatic tumor biopsies are necessary. They should determine whether or not the subsequent metastatic tumor biopsies would be required to address the secondary resistance. Under these circumstances, a single metastatic tumor biopsy is inadequate to detect the underlying clonal heterogeneity of the BC. As a solution, an analysis of ctDNA in liquid biopsies could be implemented. This can be a more efficient approach for a long-term monitoring of the molecular alterations in BC. Furthermore, the noninvasive methodology of ctDNA testing decreases the risk of complications and discomfort from biopsy procedures. This is particularly important for patients with late-stage BC.

9. A Possible Role of ctDNA in the Detection of Biomarkers for Patients with Metastatic BC

Clinicians need to keep in mind some important criteria for choosing certain CDK 4/6 inhibitors in daily practice. Since the CDK 4/6 inhibitors present similar efficacy and different safety profiles, such differences should facilitate the selection of the most appropriate medication for an individual patient. In general, the most prevalent adverse effects (AEs) of CDK 4/6 inhibitors include neutropenia (e.g., afebrile and noninfectious), anemia, thrombocytopenia, and fatigue. Due to the fact that neutropenia is the most common AE, associated with the use of CDK 4/6 inhibitors (e.g., palbociclib and ribociclib), the patients need be monitored with a complete blood cell count (CBC) prior to initiating the CDK 4/6 inhibitor, at the beginning of each therapy cycle, on day 14 of the first 2 cycles, and then, as clinically necessary. Furthermore, with ribociclib, close surveillance, especially in patients with cardiac risk factors, for the possible QT interval prolongation, cardiac arrhythmias, deep vein thrombosis, or the high risk of pulmonary embolism is required. In addition, regular electrocardiogram (ECG) monitoring, and adjusting doses of the concurrently used medications (e.g., some anti-emetic agents) is necessary. Also, elderly women with cardiac comorbidities, who might have been treated with anthracyclines for BC, require ongoing ECG assessment. In such patients, palbociclib or abemaciclib should be preferentially used over ribociclib. In addition, the potential for liver toxicity (e.g., transaminases) indicates measurement of liver function tests (e.g., alanine aminotransferase (ALT) and aspartate aminotransferase (AST)). Abemaciclib is characterized by a greater incidence of gastrointestinal symptoms (mostly diarrhea), which can be managed via anti-diarrheal agents, and a dose reduction. Also, it should be noted that abemaciclib inhibits not only CDK 4/6 but also CDK 2, and possibly CDK 9. According to the MONARCH-2 and MONARCH-3 trials, abemaciclib was found to be particularly beneficial in some patients with liver metastasis. Since abemaciclib has a different toxicity profile, compared to palbociclib and ribociclib, it can be a reasonable choice for a women, in whom it is not possible to achieve an optimal therapeutic dose with palbociclib or ribociclib (e.g., because of neutropenia). Fortunately, it is often possible to switch to a different CDK 4/6 inhibitor.
Several patients with HR-positive, HER2-negative advanced or metastatic BC, who have not been exposed to CDK 4/6 inhibitors and have been using ET, may represent a group, for which abemaciclib (as monotherapy) can be appropriate[14]. Also, the combinations of fulvestrant with palbociclib and fulvestrant with abemaciclib in the second and third therapy lines can be recommended for such patients[8, 15]. In addition, using abemaciclib alone may be considered in women, who have had prior exposure to palbociclib or ribociclib (Table 3)[26]. However, further studies are needed to examine these options in depth. After progression on a first-line AI with a CDK 4/6 inhibitor, the second-line options should be considered. In the second-line setting, it is conceivable to use a single-agent fulvestrant or a combination of fulvestrant and a CDK 4/6 inhibitor (Table 3)[26]. Some advantages from continued ET after the use of CDK 4/6 inhibitors have been reported; however, future trials in the second-line setting are needed to address this possibility. In the meantime, the use of fulvestrant (as a single-agent) or the combination of exemestane and everolimus can be considered, based on the individual patient’s characteristics. For instance, for an asymptomatic women, with a small tumor burden, long disease-free interval, or long response to prior ET, fulvestrant may be a reasonable choice. Otherwise, a combination therapy should be selected (Table 1)[17].

**Table 3.** Indications for therapy with CDK 4/6 inhibitors in women with HR-positive, HER2-negative metastatic BC[26]  

<table>
<thead>
<tr>
<th>CDK 4/6 inhibitor</th>
<th>First line therapy</th>
<th>Second line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib</td>
<td>in combination with an AI as initial ET</td>
<td>in combination with fulvestrant as ET following progression on prior ET</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>in combination with an AI as initial ET</td>
<td>in combination with fulvestrant as ET following progression on prior ET</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>in combination with an AI as initial ET</td>
<td>in combination with fulvestrant as ET following progression on prior ET, or in monotherapy</td>
</tr>
</tbody>
</table>

Abbreviations: AI, aromatase inhibitor; BC, breast cancer; CDK 4/6, cyclin-dependent kinase 4/6; ET, endocrine-based therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor

It should be emphasized that using the first-line CDK 4/6 inhibitors improves the patient’s quality of life, compared to a CHT (e.g., taxane doublet). This is particularly important, considering the main goal of extending the amount of time that a patient can use ET, and postponing the need to initiate CHT (which may involve some AE).

**11. CDK 4/6 Inhibitors in Premenopausal BC Patients**

The incidence of advanced BC among premenopausal women is increasing, and the prognosis for this group of younger women is worse, compared to the older women[27]. Furthermore, premenopausal patients with HR-positive BC are often underrepresented in clinical trials. In result, therapeutic strategies in the premenopausal population are commonly extrapolated from the data derived from postmenopausal women[29]. The scarcity of data in premenopausal patients may have an impact on the gap between treatment guidelines, and “real-world” practice. Since the underlying biology of BC in premenopausal women differs from postmenopausal women, therapeutic strategies should be directly explored among premenopausal patients[26]. It should be noted that the premenopausal women with HR-positive metastatic BC have had limited therapeutic options comparing to the postmenopausal women. Recently, palbociclib (as the first representative of CDK 4/6 inhibitors) was investigated and approved in the younger patient population. Subsequently, a some phase 3 trials have investigated CDK 4/6 inhibitors in premenopausal patients with HR-positive/HER2-negative advanced BC[11]. The findings of the first of them, the MONALEESA-7 trial (evaluating ribociclib plus ET), have revealed that the median PFS was 23.8 months in the ribociclib arm (which is the longest PFS in this patient population) (Table 1)[11]. These results, together with the findings from a subgroup of premenopausal women with ovarian function suppression (e.g., based on the PALOMA-3 and MONARCH-2 trials) have also revealed that there is a clinical advantage of adding a CDK 4/6 inhibitor to ET for the premenopausal patients[8, 13]. According to the above data, ET (with or without a CDK 4/6 inhibitor) has been the recommended approach for premenopausal patients with HR-positive advanced BC (with the addition of ovarian function suppression)[26].

**12. CDK 4/6 Inhibitors in Postmenopausal and Elderly BC Patients**

An analysis of pooled data from PALOMA 1, 2, and 3 trials was performed to assess the clinical outcomes in older patients with HR-positive/HER2-negative advanced BC[36]. According to this evaluation, out of 528 women treated with palbociclib plus letrozole, and out of 347 - treated with palbociclib plus fulvestrant, about 40%, and 25%, respectively, were aged 65 years or older. Compared to ET alone, the median PFS was significantly improved in elderly patients (over 65 years of age), who received palbociclib plus letrozole, or palbociclib plus fulvestrant. In addition, patient-reported functional status and quality of life (QoL) were satisfactory. Serious adverse effects,
such as febrile neutropenia or myelosuppression were uncommon. In general, palbociclib in combination with ET turned out to be an effective, and well-tolerated therapeutic strategy, among elderly patients with HR-positive/HER2-negative, advanced BC\(^{[30]}\).

13. Future Research Directions and Key Questions Related to the CDK 4/6 Inhibitors

The knowledge related to patterns of resistance to ET and the estimated time, when such a resistance may take place, should facilitate therapeutic decision-making. For instance, patients who present with de novo metastatic BC, and those, who progress one year or longer from the end of their adjuvant ET, can be eligible for the first-line ET\(^{[17, 31]}\). In general, a CDK 4/6 inhibitor plus an AI represent a suitable strategy for many patients with HR-positive/HER2-negative, advanced BC. Single-agent treatment with fulvestrant or an AI alone may be an adequate option for selected women with very limited disease burden, late relapse, or for those, who are unable to tolerate combination treatment\(^{[17, 31]}\). Patients who progress within one year of completing adjuvant ET are eligible for subsequent-line ET. Moreover, a combination of fulvestrant and CDK 4-6 inhibitors, as well as exemestane and everolimus can also be beneficial. It is expected the ongoing PARSIFAL trial will address a specific question of the optimal frontline therapy in patients with ER-positive/HER2-negative locally advanced or metastatic BC (NCT02491983) (ClinicalTrials.gov. PARSIFAL 2018)\(^{[32]}\). At present, answers to the following questions, related to the CDK 4/6 inhibitors, are urgently needed:

- how to detect which patients will benefit from the ET alone, considering the potential AEs of CDK 4/6 inhibitors?

- can the CDK 4/6 inhibitors be beneficial as the adjuvant or neo-adjuvant therapy?

- how to identify biomarkers of response and resistance to CDK 4/6 inhibitors?

- is it possible to find biomarkers, which will demonstrate some specific advantages of one CDK 4/6 inhibitor over another?

- is there any “optimal” sequence for using CDK 4/6 inhibitors in patients with the HR-positive/HER2-negative metastatic BC?

14. Conclusion

CDK 4/6 inhibitors as a class represent a remarkable step forward on the therapeutic landscape for patients with HR-positive/HER2-negative advanced or metastatic BC (including those, who progressed on ET). Palbociclib, ribociclib, and abemaciclib have changed the treatment algorithm for such patients. These medications are characterized by similar prolongation of PFS, and by different dosages and AEs. The mechanism of action of the CDK4/6 inhibitors is directly related to cell cycle and cell division, in terms of targeting cellular proliferation. In particular, these agents prolong the period of time, during which, the patients can use ET. In summary, the CDK 4/6 inhibitors have been recommended in combination with ET, as the first-line treatment for both premenopausal and postmenopausal patients with HR-positive/HER2-negative advanced or metastatic BC. There is a realistic hope that on-going and future trials will shed some light on potential biomarkers and sequences for using CDK 4/6 inhibitors in patients with the HR-positive/HER2-negative metastatic BC.

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